EMORD & ASSOCIATES, P.C.

BURKE PROFESSIONAL CENTER
5282 LYNGATE COURT
BURKE, VIRGINIA 22015

1050 SEVENTEENTH STREET, N.W.
SUITE 600
WASHINGTON, DC 20036

PHONE: (202) 466-6937 • FAX: (202) 466-6938
WEB SITE: www.emord.com
E-MAIL: JEMORD@EMORD.COM

3374 '02 JAN 28 A10:23

November 19, 2001

VIA TELECOPIER
AND VIA UPS OVERNIGHT
Daniel E. Troy
Chief Counsel
Food & Drug Administration
5600 Fishers Lane, GCF-1
Room 6-57
Rockville, MD 20857

Re: Health Claim: Omega-3 Fatty Acids and Coronary Heart Disease (Docket No. 91N-0103)

Dear Mr. Troy:

We represent the plaintiffs in *Pearson v. Shalala*. In this letter we seek a prompt reconsideration of a letter ruling issued by the agency on October 31, 2000, in the above-referenced case. Our clients seek agency action on or before December 31, 2001. Our clients will refrain from taking legal action against the agency until January 2002 to afford the agency sufficient time to reconsider its letter ruling. The grounds for reconsideration follow.

The United States Court of Appeals for the D.C. Circuit held FDA's suppression of the following health claim unconstitutional under the First Amendment: "Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease." *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999), *reh'g denied en banc*, 172 F.3d 72 (D.C. Cir. 1999). On the evidence before it, the Court held the claim not inherently misleading but, at worst, potentially misleading. Consistent with commercial speech precedent, the Court prohibited outright suppression of the claim and mandated evaluation of a reasonable disclaimer as a less restrictive alternative to suppression. On remand, the FDA disobeyed the Court's order. While leaving unrebutted the scientific proof in support of the claim, the agency nevertheless chose not to evaluate disclaimers as less restrictive alternatives to suppression but to rewrite the claim in its entirety. In its October 31, 2000 letter ruling, the agency informed plaintiffs that it would not allow use of the remanded claim but

91N-0103 LET 5

would refrain from taking enforcement action against them, at least for the time being, if they used the following claim of the agency's creation:

> The scientific evidence about whether omega-3 fatty acids may reduce the risk of coronary heart disease (CHD) is suggestive, but not conclusive. Studies in the general population have looked at diets containing fish and it is not known whether diets or omega-3 fatty acids in fish may have a possible effect on a reduced risk of CHD. It is not known what effect omega-3 fatty acids may or may not have on risk of CHD in the general population.

The plaintiffs' scientific advisers (as well as other scientists who study omega-3 fatty acids and coronary heart disease) have informed plaintiffs that the revised claim (1) fails to summarize accurately the current state of scientific knowledge concerning the effect of omega-3 fatty acids on coronary heart disease and (2) misleads the public by suggesting that the scientific evidence in favor of the claim is far weaker than it actually is. Indeed, the revised claim is confusingly worded, making it difficult not only for the public but also for scientific experts to discern its meaning. Moreover, the plaintiffs find the revised claim far too lengthy to fit on the labels of their dietary supplements. The plaintiffs have received word from several in the industry and in trade associations who have voiced the same concerns about the revised claim.

Consider the first sentence of the revised claim: "The scientific evidence about whether omega-3 fatty acids may reduce the risk of coronary heart disease (CHD) is suggestive, but not conclusive." That sentence misleads, according to our scientific advisers, because the evidence associating omega 3 fatty acids with reduced risk of CHD is strong, not merely suggestive. There is a substantial body of well-designed human clinical trials linking omega-3 fatty acids with reduced risk of coronary heart disease through a well-accepted mechanism of action. The statement that the evidence is merely "suggestive" misleads the public.

Consider the second sentence of the revised claim: "Studies in the general population have looked at diets containing fish and it is not known whether diets or omega-3 fatty acids in fish may have a possible effect on a reduced risk of CHD." The scientific evidence upon which plaintiffs have relied includes studies identifying the omega-3 fatty acids in fish (and, indeed, cold water fish having high levels of omega-3 fatty acids, as opposed to all fish in general) as the agent linked to the reduced CHD risk. Moreover, studies on omega-3 fatty acid supplements provide corroboration for the effect of that ingredient on reduced CHD risk. That evidence is generally accepted in the scientific community. Consequently, the entire second sentence of the revised claim is false and misleads the public.

Consider the third sentence of the revised claim: "It is not known what effect omega-3 fatty acids may or may not have on risk of CHD in the general population." The scientific studies upon which plaintiffs have relied provide evidence of the same mechanism of action causing CHD risk reduction in at risk populations as it does for individuals not suffering from illness. The evidence strongly favors the conclusion that

omega-3 fatty acids may reduce the risk of CHD in the general population. There is no sound evidence to the contrary. Consequently, the entire third sentence of the revised claim misleads the public.

Taken as a whole, the revised claim conveys a confusing (and conflicting) set of messages. In the first sentence, it appears to suggest that there is a link between omega-3 fatty acids and reduced risk of CHD but in the remaining sentences it conveys the impression that there is not sufficient evidence to support such a link. It is thus inherently misleading, contradictory, and confusing. The agency should therefore reconsider its position.

The *Pearson* plaintiffs ask the agency to reconsider its letter ruling in light of Judge Kessler's final and binding decisions in *Pearson v. Shalala*, 130 F.Supp.2d 105 (D.D.C. 2001) (*Pearson* II) and in *Pearson v. Thompson*, 141 F.Supp.2d 105 (D.D.C. 2001). Those cases establish clearly that the approach taken by FDA in its remand consideration of the omega-3 fatty acid health claim violates the mandate of our federal courts in *Pearson* I, II, and III. The decisions in *Pearson* I, II, and III establish that there is a weighty constitutional presumption in favor of disclosure over suppression, requiring FDA to accept disclaimers as the rule in instances where claims are backed by credible evidence (even when that evidence is inconclusive) and to resort to suppression only when the weight of the evidence opposes the claim and the claim is incurable by disclaimer. Here, by contrast, FDA has suppressed the remanded claim outright and has elected not to rely on a disclaimer but to rewrite the claim in its entirety, fundamentally changing its original terms and meaning. Indeed, the revised claim is largely incomprehensible due to its conflicting content and completely emasculates the scientific message that consumers so urgently need to receive (i.e., that omega 3 fatty acids may reduce the risk of coronary heart disease). As the Courts in *Pearson* I, II, and III have explained, the presence of credible evidence means that a claim is not inherently misleading. *Pearson* I, 164 F.3d at 659; *Pearson* II, 130 F.Supp.2d at 114; *Pearson* III, 141 F.Supp.2d at 111. As such, it cannot be banned outright; the constitutional remedy is to rely on disclaimers; not claim suppression. *Pearson* I, 164 F.3d at 657; *Pearson* II, 130 F.Supp.2d at 113; *Pearson* III, 141 F.Supp.2d at 111.

Moreover, the Court in *Pearson* II and III has twice instructed the FDA to rely on short, succinct and accurate disclaimers as opposed to the lengthy and entirely unusable revised claim it has chosen in this case. We offer the following as an alternative acceptable to the *Pearson* plaintiffs that complies with the Courts' rulings and conveys accurately the state of the scientific evidence.[1]

> Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease. The scientific evidence supporting this claim is strong but not conclusive.[2]

---

[1] To be sure, as the *Pearson* plaintiffs have reiterated many times in the past, they would be willing to accept any reasonable disclaimer for use with their claim.

[2] This claim may be used on any product containing at least 600 mg but not more than 2000 mg per day of DHA plus EPA.

The above claim is quite conservative in view of the widespread consensus in the scientific community that EPA and DHA do substantially reduce the risk of death due to cardiovascular disease. See, e.g., Exhibit A (W. Connor, "n-3 Fatty Acids from fish and fish oil; panacea or nostrum?" *Am J Clin Nutr* 2001; 74:415-6; "n-3 Fatty Acids and cardiovascular disease risk factors among the Inuit of Nunavik," *Am J Clin Nutr* 2001; 74: 464-73).

The plaintiffs remind the agency that it has maintained its suppression of plaintiffs' original claim since 1994. In light of FDA's First Amendment burden of proof and the constitutional command that FDA proceed expeditiously, *Elrod v. Burns*, 427 U.S. 347, 373 (1976) ("The loss of First Amendment freedoms, for even minimal periods of time, unquestionably constitutes irreparable injury"), we ask the agency to issue its written decision no later than the end of the month of December, 2001.

Sincerely,

Jonathan W. Emord
Counsel to the
Pearson plaintiffs

EXHIBIT A

See corresponding article on page 464.

n−3 Fatty acids from fish and fish oil: panacea or nostrum?[1-3]

William E Connor

The steps in the development of important medical discoveries rest first on intuition and then on associations of a certain factor with a disease, followed by scientifically designed experiments. The history of the importance of the n−3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) illustrates this point beautifully. Early Arctic explorers commented on the rarity of coronary artery disease in Eskimos despite their consumption of a very-high-fat, high-cholesterol diet. This finding was indeed a paradox until it was resolved by 2 Danish scientists, Bang and Dyerberg (1). When these investigators looked at the coronary mortality statistics in Greenland Eskimos and in Danish persons living in Greenland but having a vastly different lifestyle, they found few deaths from coronary artery disease in Greenland Eskimos but many deaths in Danes. The answer to this riddle came from an analysis of the diet of the Eskimos compared with that of the Danes (1). The latter group ate a diet high in saturated fat and cholesterol from meat and dairy products similar to the diet eaten in the homeland of Denmark. The Eskimos, on the other hand, ate seal, whale, and fish, all of which are extremely rich in EPA and DHA. This was in contrast with the lower n−3 fatty acid content of the typical Danish diet. In the Greenland Eskimos also, the content of these same n−3 fatty acids in the blood was high (2), and the tendency of the blood to form thrombi was lessened because the n−3 fatty acids were taken up by the blood platelets (3).

The same situation prevails in present-day Eskimos, as illustrated by the study by Dewailly et al (4) in this issue of the Journal. The Nunavik Inuit of Quebec, despite some Westernization, still partly consume the diet of their ancestors, which is rich in fish and marine mammals. Mortality from coronary artery disease in the Inuit is 50% less than that in the Quebec province as a whole. The Inuit's high blood content of EPA and DHA reflects their consumption of these foods from the sea.

Why the n−3 fatty acids from fish and marine oils prevent coronary artery disease has now been delineated in hundreds of experiments in animals and tissue culture cells and in population and clinical trials (5). Of the nutritional modalities thought to prevent heart disease, the evidence for the efficacy of n−3 fatty acids is strong. This evidence may be best summarized in Table 1 and by answering the following question: have other population studies and clinical trials shown that fish consumption is associated with a lowered incidence of coronary artery disease? Japanese, Dutch, and US studies indicate that deaths from coronary artery disease are reduced by ≥50% by the consumption of 1–2 fish meals/wk (6–8). The most important finding is of a reduction in sudden death from ventricular fibrillation and tachycardia. About 300000 such deaths occur in the United States each year. Direct clinical trials of fish and fish oil have also shown a striking reduction in sudden deaths (9, 10); these findings have great public health significance. Furthermore, animal studies and experiments in isolated myocytes showed that ventricular arrhythmias are inhibited by EPA, which affects sodium and calcium ion channels in the heart (11).

Thrombosis is a major complication of coronary atherosclerosis and leads to myocardial infarction. The n−3 fatty acids from fish oil have powerful antithrombotic actions. EPA inhibits the synthesis of thromboxane A_2 from arachidonic acid in platelets. Thromboxane A_2 causes platelet aggregation and vasoconstriction. By blocking thromboxane A_2 synthesis, fish oil ingestion by humans increases the bleeding time and decreases the number of platelets that stick to glass beads (12). In addition, administration of fish oil enhances the production of prostacyclin, a prostaglandin that produces vasodilation and less sticky platelets. In an in vivo baboon model, dietary fish oil prevented platelet deposition in a plastic vascular shunt (13). Injury to the intima of the carotid artery of the baboon invariably caused a marked proliferative and inflammatory lesion, greatly thickening the wall. When the animals were fed fish oil, this damage and intimal thickening were completely blocked.

The EPA and DHA contained in fish oil inhibit the development of atherosclerosis. There is evidence in both pigs and monkeys that dietary fish oil prevents atherosclerosis by actions other than the lowering of plasma cholesterol concentrations (14). These actions may be associated with the inhibition of monocyte migration into the plaque, with less cytokine and interleukin 1α production, and with stimulation of the endothelial production of nitric oxide.

Dyerberg and Bang also found that the blood of Greenland Eskimos had lower triacylglycerol and cholesterol concentrations, particularly triacylglycerol, than the blood of Danes (2). Dewailly et al (4) found that n−3 fatty acids in the plasma phospholipids of Nunavik Inuit were positively associated with HDL-cholesterol concentrations and inversely associated with

[1] From the Division of Endocrinology, Diabetes, and Clinical Nutrition, the Department of Medicine, Oregon Health & Science University, Portland.

[2] Supported by the Oregon Health & Science University Foundation and the General Clinical Research Centers Program (RR-59) of the Division of Research Resources of the National Institutes of Health.

[3] Address reprint requests to WE Connor, Department of Medicine, L463, Oregon Health & Science University, Portland, OR 97201. E-mail: connorw@ohsu.edu.

TABLE 1
Actions of n−3 fatty acids to prevent coronary heart disease and sudden death

1) Prevent cardiac arrhythmias (ventricular tachycardia and fibrillation)
2) Act as antithrombotic agents
3) Inhibit the growth of atherosclerotic plaques
4) Act as antiinflammatory agent (inhibit synthesis of cytokines and mitogens)
5) Stimulate endothelial-derived nitric oxide
6) Lower plasma concentration of triacylglycerol and VLDL cholesterol and increase plasma concentrations of HDL cholesterol

plasma triacylglycerol and the ratio of total to HDL cholesterol. These Inuit had higher n−3 fatty acid (EPA+DHA) concentrations in their plasma phospholipids proportional to the intakes of typical Eskimo marine foods. However, plasma total and LDL-cholesterol concentrations correlated positively with n−3 fatty acid concentrations. The divergent effects of n−3 fatty acids to reduce plasma triacylglycerol and elevate LDL may be explained by a dietary background high in cholesterol and saturated fat as well as in n−3 fatty acids. The 2 situations are completely compatible. In a feeding experiment by Nordoy et al (15), a diet high in n−3 fatty acids but also high in cholesterol and saturated fat decreased plasma triacylglycerol and VLDL and at the same time increased plasma LDL. The optimal diet would be one high in n−3 fatty acids and low in cholesterol and saturated fat, thus reducing both triacylglycerol and LDL concentrations in the plasma.

This pronounced effect of fish oil on hyperlipidemia is especially well documented by precise dietary studies in which a diet rich in salmon oil was fed and contrasted with a vegetable oil diet and a diet high in saturated fat (16). Fish oil lowers plasma triacylglycerol concentrations by inhibiting the synthesis of triacylglycerol and VLDL in the liver. Apolipoprotein B production is lower after consumption of fish oil than after consumption of vegetable oils such as safflower or olive oil. This mechanism of action is further substantiated by cultures of rabbit and rat hepatocytes in which EPA, for example, in contrast with oleic acid, inhibited triacylglycerol synthesis and stimulated the synthesis of membrane phospholipid.

Pronounced postprandial lipemia occurs after the absoprtion of fat from diets with high fat contents. Postprandial lipoproteins are known to be atherogenic. They are also thrombogenic because postprandial lipemia increases activated factor VII, a procoagulant. Pretreatment with fish oil greatly lessens postprandial lipemia (17), and this effect should be considered both anti-atherogenic and anti-thrombotic.

The emphasis on fish and fish oil for coronary prevention does not mean that vegetarians could not benefit from the consumption of n−3 fatty acids. The precursor to EPA and DHA in the n−3 fatty acid synthetic pathway is α-linolenic acid (18:3n−3), which is especially rich in certain vegetable oils such as canola, soy, flaxseed, and walnut oils. In the Lyon Heart Study, which emphasized linolenic acid consumption from canola margarine, blood EPA concentrations increased and the death rate from coronary artery disease was reduced by 70% with a concomitant reduction in sudden death (18). A vegetarian diet, then, can still benefit from an increased n−3 fatty acid content.

In summary, n−3 fatty acids from fish and fish oil are natural food substances that prevent coronary artery disease and sudden death. Physicians should become acquainted with the powerful therapeutic potential of these fatty acids. n−3 Fatty acids have immense public health significance for the control of the current coronary epidemic.

REFERENCES

1. Bang HO, Dyerberg J. The composition of food consumed by Greenlandic Eskimos. Acta Med Scand 1973;200:69–73.
2. Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. Am J Clin Nutr 1975;28:958–66.
3. Dyerberg J, Bang HO. Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. Lancet 1979;2:433–5.
4. Dewailly E, Blanchet C, Lemieux S, et al. n−3 Fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik. Am J Clin Nutr 2001;74:464–73.
5. Connor WE. n−3 Fatty acids and heart disease. In: Kritchevsky D, Carroll KK, eds. Nutrition and disease update: heart disease. Champaign, IL: American Oil Chemist's Society, 1994:7–42.
6. Siscovick DS, Raghunathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n−3 polyunsaturated fatty acids and the risk of primary cardiac arrest. JAMA 1995;274:1363–7.
7. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. JAMA 1998;279:23–8.
8. Kromhout D, Bosschieter EB, Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985;312:1205–9.
9. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989;2:757–61.
10. GISSI Prevenzione Investigators. Dietary supplementation with n−3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione Trial. Lancet 1999;354:447–55.
11. Kang JX, Leaf A. Antiarrhythmic effects of polyunsaturated fatty acids. Circulation 1996;94:1774–80.
12. Goodnight SH Jr, Harris WS, Connor WE. The effects of dietary omega-3 fatty acids upon platelet composition and function in man: a prospective, controlled study. Blood 1981;58:880–5.
13. Harker LA, Kelly AB, Hanson SR, et al. Interruption of vascular thrombus formation and vascular lesion formation by dietary n−3 fatty acids in fish oil in non human primates. Circulation 1993;87:1017–29.
14. Davis HR, Bridenstine RT, Vesselinovitch D, Wissler RW. Fish oil inhibits development of atherosclerosis in rhesus monkeys. Arteriosclerosis 1987;7:441–9.
15. Nordoy A, Hatcher LF, Ullmann DL, Connor WE. Individual effects of dietary saturated fatty acids and fish oil on plasma lipids and lipoproteins in normal men. Am J Clin Nutr 1993;57:634–9.
16. Phillipson BE, Rothrock DW, Connor WE, Harris WS, Illingworth DR. Reduction of plasma lipids, lipoproteins, and apoproteins by dietary fish oils in patients with hypertriglyceridemia. N Engl J Med 1985;312:1210–6.
17. Harris WS, Connor WE, Alam N, Illingworth DR. The reduction of postprandial triglyceridemia in humans by dietary n−3 fatty acids. J Lipid Res 1988;29:1451–60.
18. De Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 1994;343:1454–9.

n−3 Fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik[1–3]

Eric Dewailly, Carole Blanchet, Simone Lemieux, Louise Sauvé, Suzanne Gingras, Pierre Ayotte, and Bruce John Holub

ABSTRACT

Background: Inuit traditionally consume large amounts of marine foods rich in n−3 fatty acids. Evidence exists that n−3 fatty acids have beneficial effects on key risk factors for cardiovascular disease.

Objective: Our goal was to verify the relation between plasma phospholipid concentrations of the n−3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and various cardiovascular disease risk factors among the Inuit of Nunavik, Canada.

Design: The study population consisted of 426 Inuit aged 18–74 y who participated in a 1992 health survey. Data were obtained through home interviews and clinical visits. Plasma samples were analyzed for phospholipid fatty acid composition.

Results: Expressed as the percentage of total fatty acids, geometric mean concentrations of EPA, DHA, and their combination in plasma phospholipids were 1.99%, 4.52%, and 6.83%, respectively. n−3 Fatty acids were positively associated with HDL-cholesterol concentrations and inversely associated with triacylglycerol concentrations and the ratio of total to HDL cholesterol. In contrast, concentrations of total cholesterol, LDL cholesterol, and plasma glucose increased as n−3 fatty acid concentrations increased. There were no significant associations between n−3 fatty acids and diastolic and systolic blood pressure and plasma insulin.

Conclusions: Consumption of marine products, the main source of EPA and DHA, appears to beneficially affect some cardiovascular disease risk factors. The traditional Inuit diet, which is rich in n−3 fatty acids, is probably responsible for the low mortality rate from ischemic heart disease in this population. *Am J Clin Nutr* 2001;74:464–73.

KEY WORDS n−3 Fatty acids, eicosapentaenoic acid, docosahexaenoic acid, fish intake, cardiovascular disease, risk factor, cholesterol, LDL, HDL, triacylglycerol, blood pressure, glucose, insulin, Natives, Inuit

See corresponding editorial on page 415.

INTRODUCTION

Diets rich in fish and marine mammals have been linked to a lower incidence of thrombotic disease in Greenland and Japan (1, 2). Dietary fish and marine oils are rich in eicosapentaenoic acid (EPA; 20:5n−3) and docosahexaenoic acid (DHA; 22:6n−3), which are long-chain polyunsaturated fatty acids of the n−3 series. n−3 Fatty acids favorably affect risk factors implicated in the pathogenesis of atherosclerotic and thrombotic diseases (3–6). Epidemiologic evidence also exists for an inverse relation between fish consumption and death from ischemic heart disease (IHD) (7–12). Higher concentrations of EPA and DHA in plasma and serum phospholipids are inversely correlated with cardiovascular disease (CVD) and IHD (13, 14).

Located in a vast a territory of ≈563 515 km² north of the 55th parallel, the Inuit population of Nunavik (northern Quebec) is estimated at 8970 persons and is distributed among 14 coastal villages (15). Compared with the rest of Canada, the Inuit population is very young. In 1991, 40% of the Inuit were ≤15 y of age and 2% were ≥65 y, compared with 20% and 11%, respectively, of the remaining Canadian population (16). Inuit are confronted with challenging environmental conditions such as extreme cold; historically, the abundance of arctic fauna has supported the survival of this population. The traditional diet consists primarily of marine mammals (white whale (beluga) and seal), fish, and caribou, which are eaten fresh (raw or cooked) or dried, with use of the skin, blubber, liver, and fat in different meals.

In 1992 daily intakes of n−3 fatty acids from traditional food, especially fish, marine mammals, and piscivorous wildfowl, were high among Inuit persons compared with intakes by other populations (2, 17, 18). However, strong evidence exists of a decrease in traditional food consumption by the Inuit, primarily from 1950 to 1970, when Inuit populations settled into permanent communities and market foods became increasingly available (18, 19). In several native populations, a shift away from traditional lifestyles and diets is associated with an increased prevalence of risk factors for CVD, such as high blood pressure, elevated blood lipids, diabetes, and obe-

[1] From the Public Health Research Unit, CHUL Research Center, Centre Hospitalier Universitaire de Quebec, Ste-Foy, Canada; the Departments of Social and Preventive Medicine and of Food Sciences and Nutrition, Laval University, Ste-Foy, Canada; and the Department of Human Biology and Nutritional Sciences, the University of Guelph, Guelph, Canada.

[2] Supported by Indian and Northern Affairs Canada.

[3] Address reprint requests to E Dewailly, Laval University Medical Research Center, 2400 d'Estimauville, Beauport, Quebec G1E 7G9, Canada. E-mail: eric.dewailly@crchul.ulaval.ca.

Received November 22, 2000.

Accepted for publication April 16, 2001.

Am J Clin Nutr 2001;74:464–73. Printed in USA. © 2001 American Society for Clinical Nutrition

sity (20–23). Additionally, evidence points to increasing rates of death from IHD and stroke among native populations. In this study, we examined the n−3 fatty acid status of a representative sample of Nunavik Inuit and verified the relation between plasma phospholipid concentrations of n−3 fatty acids and various CVD risk factors.

SUBJECTS AND METHODS

Study design

In 1992 Santé Québec, an organization of the Quebec Health and Social Services Ministry, conducted a health survey among the Inuit population of Nunavik as part of the federal-provincial Canadian Heart Health Initiative. The primary objective of the survey was to collect relevant information on the physical, social, and psychosocial health of the Inuit population (24). This information was gathered in several stages. First, face-to-face interviews were conducted at each participant's home to administer a lifestyle questionnaire. Among the same participants, a clinical session was conducted in the village health clinic to obtain physiologic and anthropometric measurements. Finally, a face-to-face interview was conducted by a nurse to collect 24-h recalls of dietary intake. A food-frequency questionnaire was administered only to women who were neither pregnant nor breast-feeding. Stored plasma samples were used to measure the fatty acid composition of plasma phospholipids. Samples were stored at −80°C for ≤4 mo. Our team was responsible for analyzing the fatty acids and contaminants in the blood samples. Information on demographic characteristics, the prevalence of CVD risk factors, and food intake was obtained from the Santé Québec data files.

Study population

The target population of the survey comprised all permanent residents of Nunavik aged 18–74 y, excluding households consisting of only non-Inuit persons and persons not related to an Inuit and excluding institutionalized persons (24). The population was stratified according to the 14 villages and the sample was stratified by village, with the quasiproportional representation of the number of households in each stratum. The Quebec Bureau of Statistics chose a design that would afford an acceptable degree of precision for any prevalence ≥10% for all communities combined. Of the household respondents, 492 participants underwent the clinical measurements and blood tests. Of these 492 Inuit, 66 did not fast for ≥12 h before blood sampling and were therefore excluded. The study protocol was approved by the Ethics Committee of Maisonneuve-Rosemont Hospital (Montreal).

Plasma lipids, glucose, and insulin

Concentrations of plasma total cholesterol, triacylglycerols, LDL cholesterol, and HDL cholesterol were analyzed according to the methods of the Lipid Research Clinics (25). Cholesterol and triacylglycerol concentrations were measured in plasma and in lipoprotein fractions with use of an Auto-Analyzer II (Technicon Instruments Corporation, Tarrytown, NY). The HDL fraction was obtained after precipitation of LDL in the infranatant fluid with heparin and manganese chloride. Plasma glucose was measured enzymatically and fasting insulin concentrations were measured with a commercial double-antibody radioimmunoassay (LINCO Research, St Louis) that showed little cross-reactivity (<0.2%) with human proinsulin and for which CVs were ≤5.5% (26).

Plasma phospholipid fatty acids

To measure the fatty acid composition of plasma phospholipids, 200-μL plasma samples were extracted after the addition of chloroform:methanol (2:1, by vol) in the presence of a known amount of internal standard (diheptadecanoyl phospholipid) (27). The total phospholipid was isolated from the lipid extract by thin-layer chromatography with heptane:isopropyl ether:acetic acid (60:40:3, by vol) as the developing solvent. After transmethylation with boron trifluoride:methanol, the fatty acid profile was determined by capillary gas liquid chromatography. Fatty acid concentrations in plasma phospholipids were expressed as percentages of the total area of all fatty acid peaks from 14:0 to 24:1. In this study, plasma phospholipid concentrations of fatty acids correspond to relative percentages of total fatty acids by weight.

Blood pressure

Four blood pressure measurements were taken by a trained survey nurse according to the recommendations of the Consensus Conference on the Management of Mild Hypertension in Canada (28). Standard mercury sphygmomanometers, 38-cm (15-in) stethoscopes, and appropriately sized cuffs were used. Pressure readings were taken at the beginning and at the end of both the home interviews and the clinical visits. These values are reported as the arithmetic mean of the 4 readings.

Lifestyle assessment and anthropometry

Lifestyle habits (alcohol consumption, smoking status, etc) were assessed by questionnaire during a face-to-face interview. Height, weight, and waist and hip girth were measured during the clinical session. Waist girth was measured by positioning the measuring tape horizontally at the level of noticeable waist narrowing and recording the circumference to the nearest centimeter. The mean (±SD) body mass index (BMI; in kg/m^2) of the subjects was 26.7 ± 4.9, their mean waist girth was 86.0 ± 13.1 cm, and the correlation coefficient between these 2 indexes was 0.88 (P = 0.0001). In this study, the accumulation of adipose tissue in the abdominal area as measured by waist girth was used to measure abdominal obesity (29–31). A waist girth ≥100 cm for subjects aged <40 y and ≥90 cm for subjects aged ≥40 y was defined as abdominal obesity (32).

Dietary assessment

Data on fish and marine mammal intake were obtained with use of a 24-h dietary recall and a food-frequency questionnaire administered by a nurse (18). The 24-h dietary recall assessed the amounts of marine foods consumed by the Inuit community (men and women) the day before the survey. The food-frequency questionnaire was administered to 226 women and measured their consumption of traditional and market foodstuffs. *Traditional food* referred to 23 food items (including several parts of marine mammals such as meat, fat, skin, and liver) derived from fishing and hunting; frequency of consumption was recorded for all 4 seasons. A specific question regarding the monthly frequency of consumption of seal meat was asked of all study participants (men and women). The n−3 fatty acid content of traditional foods eaten most often by the Inuit population was determined in a previous study (19, 33).

Data analysis

All statistics presented in this paper were obtained from weighted data to reestablish the equiprobability of an individual

TABLE 1
Relative concentrations of fatty acids in plasma phospholipids in the Inuit of Nunavik[1]

Fatty acids	Arithmetic $\bar{x} \pm$ SE	Geometric $\bar{x}$	95% CI	Minimum	Maximum
		% by wt of total fatty acids			
PUFA					
n−3 Series					
Total[2]	9.71 ± 0.23	8.63	(8.23, 9.04)	2.41	29.51
EPA	3.01 ± 0.13	1.99	(1.81, 2.18)	0.09	17.27
DHA	4.95 ± 0.10	4.52	(4.33, 4.71)	0.39	11.88
EPA+DHA	7.95 ± 0.21	6.83	(6.46, 7.21)	0.58	26.50
n−6 Series					
Total[3]	28.45 ± 0.23	28.04	(27.57, 28.51)	13.12	41.12
AA	6.22 ± 0.09	5.97	(5.80, 6.14)	1.82	14.85
Total PUFA, n−3 + n−6 series	38.16 ± 0.13	38.06	(37.80, 38.33)	25.99	48.64
n−3:n−6	0.38 ± 0.01	0.31	(0.29, 0.33)	0.06	2.25
EPA:AA	0.51 ± 0.02	0.33	(0.30, 0.37)	0.01	4.77
MUFA[4]	18.21 ± 0.13	18.03	(17.79, 18.27)	11.98	29.70
SFA[5]	43.63 ± 0.15	43.52	(43.23, 43.82)	27.44	58.02
P:S	0.88 ± 0.01	0.87	(0.86, 0.89)	0.45	1.77

[1] PUFA, polyunsaturated fatty acids; EPA, eicosapentaenoic acid (20:5n−3); DHA, docosahexaenoic acid (22:6n−3); AA, arachidonic acid (20:4n−6); MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; P:S, ratio of PUFA to SFA.
[2] 18:3 + 18:4 + 20:3 + 20:4 + 20:5 + 22:5 + 22:6.
[3] 18:2 + 18:3 + 20:2 + 20:3 + 20:4 + 22:2 + 22:4 + 22:5.
[4] 14:1 + 16:1 + 18:1 + 20:1 + 22:1 + 24:1.
[5] 14:0 + 16:0 + 17:0 + 18:0 + 20:0 + 22:0 + 24:0.

being selected for the sample and to take into account nonresponse by age and sex. To this end, each respondent was given a value (weight) corresponding to the number of subjects he or she represented in the Nunavik population. Thus, all results presented in this paper were weighted and are representative of the entire Nunavik adult population (24). Crude n values are presented for information only.

In the statistical analysis we sought to first to describe the plasma phospholipid concentrations of n−3 fatty acids. Plasma and serum phospholipid fatty acid profiles are recognized as useful biomarkers for EPA and DHA status and intake (3, 34). Subjects were grouped according to biological and lifestyle factors. The statistical distribution of plasma fatty acid concentrations was first checked and was found to be skewed. Therefore, the geometric mean was used as the measure of central tendency for fatty acid concentrations. Arithmetic means were also calculated to facilitate comparisons with other surveys. Results also include 95% CIs of geometric means.

Analysis of variance (ANOVA) on the logarithm of plasma fatty acid concentrations was used to determine effect comparisons among groups. Mean daily intakes of traditional foods and of n−3 fatty acids and mean values of CVD risk factors were calculated according to age and sex. The potential interaction effect of age and sex was checked by using a two-factor ANOVA with an interaction term. The associations between the plasma phospholipid concentrations of n−3 fatty acids, particularly of EPA and DHA, and values for cardiovascular disease risk factors were assessed by use of multiple linear regression analysis. The potential interaction effect of age and sex was also checked in the regression models. Regression analyses were conducted with data from subjects who were not taking prescribed drugs for hypercholesterolemia, high blood pressure, or diabetes. Adjustments were made for potential confounding effects of age, sex, waist girth, smoking, and alcohol intake. Covariance analysis was used to calculate mean concentrations of HDL and triacylglycerols according to quintiles of EPA+DHA concentrations in plasma phospholipids. Covariance analysis was performed to control for the same confounding variables as described above and excluded the same subjects. A test for trends was performed across quintiles. All statistical analyses were performed with the SAS software package (version 6.12; SAS Institute Inc, Cary, NC (35)) and statistical significance was set at $\alpha = 0.05$.

RESULTS

The study population consisted of 426 Inuit aged 18–74 y, of whom 179 were men (mean age: 38.7 y) and 247 were women (mean age: 37.8 y). The fatty acid composition in the plasma phospholipids of the study population is shown in Table 1. The geometric mean concentrations of EPA, DHA, and their combination (EPA+DHA) were 1.99%, 4.52%, and 6.83% by wt, respectively. Nearly 25% and 66%, respectively, of the Inuit had plasma concentrations of EPA and DHA >5.0% by wt (data not shown). EPA+DHA accounted for 80% of total n−3 fatty acids and 10% of the Inuit had EPA+DHA concentrations as high as 15.0% by wt. The geometric mean concentration of total n−6 fatty acids was 28.04% by wt and arachidonic acid (AA) accounted for 21% of n−6 fatty acids. Concentrations of total n−3 and n−6 fatty acids were inversely correlated ($r = -0.81$, $P \leq 0.0001$). The ratios of EPA to AA and of n−3 to n−6 fatty acids were 0.33 and 0.31, respectively, and 20% of the Inuit had an EPA:AA >1.0. Monounsaturated and saturated fatty acids in plasma phospholipids were 18.03% and 43.52% by wt of total fatty acids, respectively. The ratio of polyunsaturated to saturated fatty acids was 0.87, and 10% of the Inuit had a ratio >1.0.

Summarized in Table 2 is the relation between relative concentrations of n−3 fatty acids and characteristics of the Inuit population. Concentrations of EPA, DHA, and EPA+DHA and the ratios of EPA to AA and of n−3 to n−6 fatty acids varied significantly according to sex, with Inuit women having higher

TABLE 2
Relative concentrations of n−3 fatty acids in plasma phospholipids according to characteristics of the Inuit population[1]

Potential confounding variables	EPA	DHA	EPA+DHA	EPA:AA	n−3:n−6
			% by wt of total fatty acids		
Sex					
Men (*n* = 179)	1.80 ± 0.19	4.12 ± 0.13	6.19 ± 0.32	0.29 ± 0.03	0.28 ± 0.02
Women (*n* = 247)	2.20 ± 0.17	4.97 ± 0.13	7.55 ± 0.27	0.38 ± 0.03	0.35 ± 0.02
P	0.03	0.0001	0.0003	0.0003	0.0003
Age					
18–39 y (*n* = 254)	1.50 ± 0.17	4.01 ± 0.11	5.76 ± 0.21	0.25 ± 0.02	0.25 ± 0.01
≥40 y (*n* = 172)	3.58 ± 0.23	5.77 ± 0.15	9.79 ± 0.35	0.59 ± 0.04	0.48 ± 0.02
P	0.0001	0.0001	0.0001	0.0001	0.0001
Waist girth					
Normal (*n* = 283)	1.83 ± 0.15	4.32 ± 0.11	6.46 ± 0.23	0.31 ± 0.03	0.29 ± 0.01
Elevated (*n* = 121)	2.68 ± 0.28	5.17 ± 0.21	8.22 ± 0.46	0.42 ± 0.05	0.40 ± 0.01
P	0.0007	0.0004	0.0002	0.01	0.0001
Smoking status					
Smoker (*n* = 248)	2.14 ± 0.16	4.58 ± 0.12	7.03 ± 0.26	0.36 ± 0.03	0.31 ± 0.02
Nonsmoker (*n* = 130)	2.01 ± 0.26	4.59 ± 0.19	6.92 ± 0.42	0.33 ± 0.04	0.32 ± 0.03
P	0.53	0.96	0.79	0.79	0.95
Alcohol intake					
None (*n* = 139)	2.41 ± 0.27	5.07 ± 0.18	7.89 ± 0.42	0.41 ± 0.05	0.36 ± 0.03
1–4 drinks/d (*n* = 61)	1.64 ± 0.34	4.23 ± 0.25	6.20 ± 0.53	0.29 ± 0.06	0.27 ± 0.03
≥5 drinks/d (*n* = 127)	2.04 ± 0.18	4.28 ± 0.15	6.58 ± 0.30	0.32 ± 0.03	0.29 ± 0.02
P	0.03	0.001	0.004	0.02	0.004
Medication for CVD problems					
Yes (*n* = 24)	2.82 ± 0.56	5.75 ± 0.39	8.98 ± 0.88	0.47 ± 0.08	0.43 ± 0.05
No (*n* = 402)	1.95 ± 0.13	4.47 ± 0.10	6.74 ± 0.21	0.35 ± 0.02	0.30 ± 0.01
P	0.11	0.02	0.03	0.12	0.02

[1] Geometric $\bar{x}$ ± SE. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid; CVD, cardiovascular disease. *P* by one-way ANOVA.

values than Inuit men. About 38% of the Inuit women had concentrations of EPA+DHA as high as 10.0% by wt; only 27% of the Inuit men had concentrations this high ($P < 0.001$; data not shown). Concentrations of n−3 fatty acids increased significantly with age, as did the ratios of EPA to AA and of n−3 to n−6 fatty acids. Concentrations of EPA ≥5.0% by wt or of DHA ≥5.0% by wt were observed mainly among Inuit aged ≥40 y (data not shown). About 85% of Inuit aged 18–39 y had total n−6 fatty acid concentrations >25.0% by wt, whereas this concentration was reached by only 48% of Inuit aged >40 y (data not shown). Subjects with high waist girths had higher concentrations of n−3 fatty acids than did subjects with normal waist girths. n−3 Fatty acid concentrations did not vary significantly according to smoking status, but alcohol abstainers had higher concentrations of EPA, DHA, and EPA+DHA and higher ratios of EPA to AA and of n−3 to n−6 than did subjects who consumed ≥1 alcoholic drink/d. Higher concentrations of DHA and EPA+DHA and a higher ratio of n−3 to n−6 fatty acids were observed in Inuit who used medications for hypercholesterolemia, high blood pressure, and diabetes than in nonusers.

Forty-one percent of the Inuit reported having eaten traditional foods the day before the survey. Mean traditional food consumption of marine origin was 131.2 g (Table 3). Quantitatively, the most popular traditional foods consumed by the Inuit were mattak (white whale skin), red char (arctic char), ringed seal meat, lake trout, and lake whitefish (data not shown). According to the 24-h dietary recall, mean intakes of EPA, DHA, and EPA+DHA from traditional foods were 1020.7, 1093.9, and 2114.6 mg, respectively. The maximum daily intake of EPA+DHA was 34.8 g. n−3 Fatty acid intakes increased significantly with age but did not vary according to sex. There was no interaction effect of age and sex when daily intakes were compared. Data from the food-frequency questionnaire completed by the Inuit women showed that mean annual daily intakes of EPA, DHA, and EPA+DHA were 576.8, 715.9, and 1292.7 mg, respectively. n−3 Fatty acid intakes were significantly higher among Inuit women aged ≥40 y than among women aged 18–30 y.

We examined the relation between concentrations of total n−3 fatty acids and the ratio of EPA to AA in plasma phospholipids and the frequency of seal meat consumption (Figure 1). In all the Inuit, as the frequency of seal meat consumption increased, the concentrations of total n−3 fatty acids and the EPA:AA increased ($P = 0.0001$).

For subsequent analyses, 20 of the 426 subjects were excluded because they reported taking medication related to CVD. In these analyses, mean concentrations of total and LDL cholesterol did not vary according to sex but increased significantly with age (Table 4). The mean HDL-cholesterol concentration was higher in women than in men and increased with age. In contrast, the ratio of total to HDL cholesterol was higher in men than in women and did not vary according to age. Mean concentrations of triacylglycerols did not vary according to sex or age. Both systolic and diastolic blood pressures were higher in men than in women and increased with age. Mean concentrations of glucose and insulin did not vary according to sex and only glucose concentrations increased significantly with age. When comparing mean values of CVD risk factors among groups, an interaction effect of age and sex was found for HDL, the ratio of total to HDL cholesterol, systolic blood pressure, and insulin.

TABLE 3
Daily intakes of marine foods, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) in the Inuit population, by sex and age[1]

	24-h Dietary recall					Food-frequency questionnaire (women only)		
Daily intakes	Men (n = 179)	Women (n = 247)	18–39 y (n = 254)	≥40 y (n = 172)	All (n = 426)	18–39 y (n = 128)	≥40 y (n = 98)	All (n = 226)
Traditional foods (g)	142.6 ± 18.3	110.6 ± 12.3	92.1 ± 11.7	205.6 ± 19.8[2]	131.2 ± 10.7	157.6 ± 14.4	175.5 ± 13.3	161.2 ± 10.0
EPA (mg)	1046.7 ± 190.8	994.4 ± 124.4	793.8 ± 128.6	1453.4 ± 198.1[3]	1020.7 ± 110.1	550.2 ± 75.6	635.3 ± 54.1	576.8 ± 48.7[4]
DHA (mg)	1149.2 ± 199.0	1038.0 ± 129.4	832.4 ± 130.6	1592.5 ± 211.5[3]	1093.9 ± 114.7	689.9 ± 109.8	773.3 ± 75.2	715.9 ± 70.1[4]
EPA+DHA (mg)	2196.0 ± 388.5	2032.4 ± 253.2	1626.1 ± 258.7	3045.9 ± 408.0[3]	2114.6 ± 224.2	1240.1 ± 184.1	1408.6 ± 127.8	1292.7 ± 117.9[4]

[1] Arithmetic $\bar{x}$ ± SE.
[2,3] Significantly different from 18–39 y (two-factor ANOVA): [2] $P \leq 0.0001$, [3] $P \leq 0.05$, [3] $P \leq 0.01$.
[4,5] Significantly different from 18–39 y (one-way ANOVA): [4] $P \leq 0.05$, [5] $P \leq 0.01$.

Shown in Table 5 are the regression coefficients (β values) from the multiple linear regression analysis with CVD risk factor values as the dependant variables and relative concentrations of n−3 fatty acids in plasma phospholipids as the predictor variable. n−3 Fatty acid concentrations were positively associated with concentrations of total, LDL, and HDL cholesterol. EPA and the ratio of EPA to AA were negatively associated with the ratio of total to HDL cholesterol. All n−3 fatty acids showed negative associations with triacylglycerol concentrations, except for DHA, for which no significant association was found. n−3 Fatty acids were not associated with diastolic or systolic blood pressures. All n−3 fatty acids were positively associated with plasma glucose. n−3 Fatty acids, especially EPA and the ratio of EPA to AA, tended to be inversely associated with plasma insulin, but this relation was not significant. No modification effect was found for age and sex on the observed associations when these relations were verified through regression analysis.

Covariance analysis was conducted to examine mean concentrations of HDL and triacylglycerols according to quintiles of EPA+DHA concentrations in plasma phospholipids. The mean concentration of HDL varied significantly according to quintiles of EPA+DHA and reached as high as 1.70 mmol/L at quintile 5 (Figure 2). The mean concentration of triacylglycerols also varied according to quintiles of EPA+DHA and was significantly lower in quintile 5 than in the lowest quintiles (Figure 3).

DISCUSSION

The plasma phospholipids of the Nunavik Inuit, who traditionally consume large amounts of marine foods, contained relatively high concentrations of n−3 fatty acids. Older Inuit had higher concentrations of n−3 fatty acids than did younger Inuit, reflecting their higher intakes of marine foods. This last observation is consistent with previous studies conducted in northern native populations (36–41). Modifications in the Inuit diet, including reductions in marine product consumption, have taken place over the past decades, especially in younger Inuit. This decline in marine food consumption is attributable in part to the greater availability of market foods in communities (19). However, n−3 fatty acid intakes among the Inuit are high compared with intakes of other populations (17). The results of a recent study suggest that traditional food consumption has not varied greatly since 1992 and that the greatest sources of n−3 fatty acids (eg, marine mammals and fish) in the Inuit diet remain popular in Nunavik today (42).

In the Inuit women, intakes of marine foods and of n−3 fatty acids measured with use of the food-frequency questionnaire appeared to be lower than those estimated with use of the 24-h dietary recall. Because food-frequency questionnaires are more appropriate for measuring regular intakes (43), it can be assumed that the n−3 fatty acid intakes of the Inuit men may have been overestimated by the 24-h dietary recall method. Indeed, the results

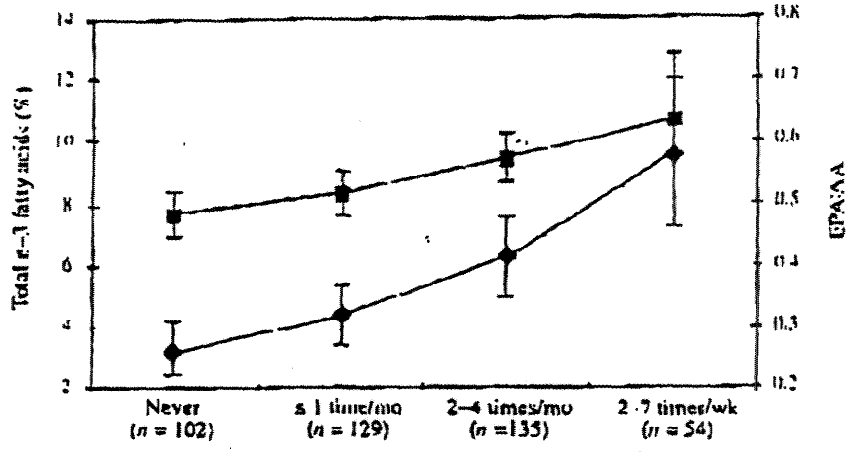

FIGURE 1. Relation between the frequency of seal meat consumption and the mean (and 95% CI) relative concentrations of total n−3 fatty acids (■) and ratio of eicosapentaenoic acid to arachidonic acid (EPA:AA) in plasma phospholipids (◆).

TABLE 4
Values of cardiovascular disease (CVD) risk factors in the Inuit population, by sex and age[1]

CVD risk factors	Men (n = 170)	Women (n = 236)	18–39 y (n = 252)	≥40 y (n = 154)	Total (n = 406)	P^2 for sex × age
TC (mmol/L)	5.04 ± 0.08	5.10 ± 0.06	4.90 ± 0.06	5.47 ± 0.07[3]	5.07 ± 0.05	0.58
LDL (mmol/L)	3.09 ± 0.07	3.00 ± 0.05	2.94 ± 0.05	3.29 ± 0.07[4]	3.04 ± 0.04	0.19
HDL (mmol/L)	1.40 ± 0.03	1.61 ± 0.03[3]	1.43 ± 0.03	1.66 ± 0.04[3]	1.50 ± 0.02	0.006
TC:HDL	3.92 ± 0.11	3.40 ± 0.07[3]	3.68 ± 0.08	3.63 ± 0.10	3.67 ± 0.06	0.008
Triacylglycerols (mmol/L)	1.22 ± 0.07	1.09 ± 0.03	1.14 ± 0.05	1.20 ± 0.06	1.16 ± 0.04	0.27
SBP (mm Hg)	115.33 ± 0.92	109.80 ± 0.83[3]	109.71 ± 0.66	119.35 ± 1.18[3]	112.60 ± 0.63	0.02
DBP (mm Hg)	76.09 ± 0.65	71.37 ± 0.53[3]	72.81 ± 0.53	76.00 ± 0.68[4]	73.76 ± 0.43	0.79
Glucose (mmol/L)	5.15 ± 0.08	5.12 ± 0.09	4.91 ± 0.04	5.64 ± 0.15[3]	5.14 ± 0.06	0.12
Insulin (pmol/L)	58.32 ± 4.87	59.14 ± 4.44	56.07 ± 3.71	65.01 ± 6.43	58.72 ± 3.27	0.005

[1] Arithmetic $\bar{x}$ ± SE. TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[2] Two-factor ANOVA.
[3,4] Significantly different from 18–39 y (two-factor ANOVA); [3] $P \leq 0.0001$, [4] $P \leq 0.001$.
[5] Significantly different from men, $P \leq 0.0001$ (two-factor ANOVA).

of a previous study documenting marine mammal consumption among the Inuit of Nunavik indicate that Inuit men and women have similar consumption patterns for traditional foods (44).

Concentrations of EPA, DHA, and total n−3 fatty acids among the Inuit of Nunavik are similar overall to those observed among Alaskan river village Eskimos but are lower than those reported for Igloolik Inuit in Nunavut (Canada) and Alaskan coastal village Eskimos (37, 45). The ratio of n−3 to n−6 fatty acids in the plasma phospholipids of Nunavik Inuit increased with age as shown in previous studies among Alaskan Eskimos, Greenland Inuit, and Inuit of the Nunavut (36, 37, 41, 45). Differences between Artic regions may be attributed to the different laboratory methods used and also to the territorial availability of fish species; populations in coastal regions consume more marine mammals and fish than do inland populations. Furthermore, traditional food intakes may vary according to the degree of urbanization of Inuit communities (46).

Our results showed a protective effect of n−3 fatty acids on HDL-cholesterol and triacylglycerol concentrations, which are key risk factors for CVD (47–50). The inverse relation noted between n−3 fatty acid intake and circulating plasma triacylglycerol concentrations is well documented (3). A positive effect of n−3 fatty acids on HDL-cholesterol concentrations has not been consistently found, but is noted mainly when large doses of n−3 fatty acids are used (3, 27, 51). Our study supports these findings. Moreover, although HDL-cholesterol concentrations tend to stabilize or decrease with age (52–54), our results showed that HDL-cholesterol concentrations increased with age among the Inuit. Thus, the elevated intake of n−3 fatty acids in the older Inuit appears to override the effect of age on HDL-cholesterol concentrations.

In this study, concentrations of EPA+DHA were positively associated with total and LDL cholesterol. The reported effects of n−3 fatty acids on both of these CVD risk factors are inconsistent (3, 55). Fish oil sometimes increases LDL-cholesterol concentrations (56, 57). Although there is still controversy regarding the effects of n−3 fatty acids on the oxidative susceptibility of LDL, n−3 fatty acids may change the composition of

TABLE 5
Regression coefficients from multiple linear regression analysis with values of cardiovascular disease (CVD) risk factors as dependent variables and relative concentrations of fatty acids in plasma phospholipid as predictor variables[1]

CVD risk factors	Log EPA	Log DHA	Log EPA+DHA	Log EPA:AA	Log n−3:n−6
TC	0.59	1.65	1.22	0.58	1.00
	(0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
LDL	0.38	1.12	0.81	0.40	0.63
	(0.005)	(0.0003)	(0.0007)	(0.002)	(0.003)
HDL	0.29	0.45	0.48	0.26	0.41
	(0.0001)	(0.004)	(0.0001)	(0.0001)	(0.0001)
TC:HDL	−0.40	−0.09	−0.50	−0.37	−0.44
	(0.04)	(0.85)	(0.14)	(0.05)	(0.14)
Log triacylglycerols	−0.15	−0.11	−0.19	−0.11	−0.15
	(0.0001)	(0.12)	(0.0003)	(0.0002)	(0.001)
SBP	−1.35	−1.02	−2.91	−1.54	−2.90
	(0.34)	(0.79)	(0.32)	(0.34)	(0.26)
DBP	−0.99	0.51	−1.66	−0.89	−1.78
	(0.41)	(0.85)	(0.44)	(0.45)	(0.34)
Glucose	0.41	1.01	0.81	0.97	0.71
	(0.02)	(0.01)	(0.008)	(0.02)	(0.008)
Log insulin	−0.08	−0.14	−0.12	−0.08	−0.10
	(0.07)	(0.18)	(0.13)	(0.06)	(0.18)

[1] P values in parentheses. Each model included age, sex, waist girth, smoking status, and alcohol intake. n = 406. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

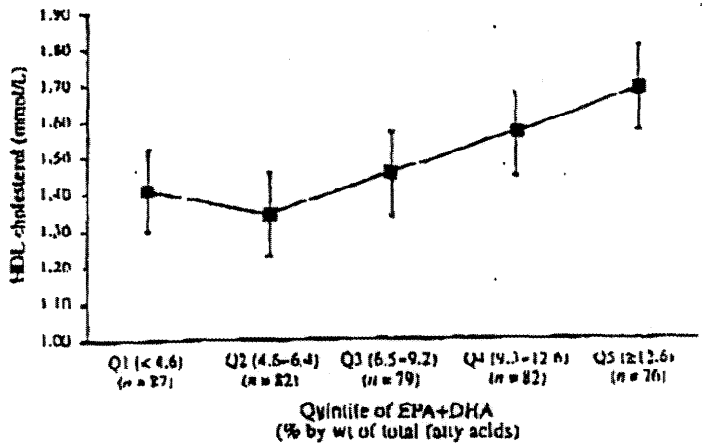

FIGURE 2. Mean (and 95% CI) concentrations of HDL cholesterol according to quintile of eicosapentaenoic plus docosahexaenoic acid (EPA+DHA) concentrations in plasma phospholipids. *P* for trend = 0.0002.

LDL, leading to less atherogenic LDL particles with lower phospholipid and apolipoprotein B concentrations and a higher LDL particle size (58–61). It was also suggested that combining an antioxidant with n−3 fatty acids may protect against oxidative stress (57, 61, 62). The results of one study showed that reduced LDL-cholesterol concentrations combined with antioxidant therapy improve impaired endothelium-dependent coronary vasodilatation (63). LDL atherogenicity may be influenced by the presence of antioxidants such as vitamins A and E and perhaps selenium, which inactivate the atherosclerotic properties of LDL (57, 64–66). In the course of the Santé Québec Health Survey, we measured plasma concentrations of selenium in a subsample of 40 Inuit. These subjects had higher selenium concentrations ($\bar{x}$: 2.0 μmol/L) than reported for other general populations (≈1 μmol/L) (44). White whale skin (mattak) is especially rich in selenium (5.5 μg/g) and is consumed by the Inuit in large amounts when it is available (33). Suadicani et al (67) reported an increased risk of IHD in Danes who had serum selenium concentrations ≤1 μmol/L. In a 7-y follow-up study, Salonen (68) found an excess risk of death by coronary disease and CVD and an excess risk of myocardial infarction among subjects with low selenium concentrations. Thus, we can postulate that the paradoxical finding regarding the increase in LDL with increasing n−3 fatty acid concentrations in plasma phospholipids may reflect, among the Inuit, an increase in LDL particle size. The antioxidant action of selenium, which enhances the antiatherogenic properties of n−3 fatty acids, may also explain the reduced mortality rate from IHD among the Inuit of Nunavik.

We found no relation between n−3 fatty acids and plasma pressure. Morris et al (69) reported that the hypotensive effect of high doses of fish oil may be strongest in hypertensive subjects and in those with clinical atherosclerotic disease or hypercholesterolemia. Most studies that targeted healthy individuals with no clinical manifestation of hypertension failed to detect a hypotensive effect of n−3 fatty acids on blood pressure (69–72). Nearly 6% of the Inuit had high blood pressure, compared with ≈14% of

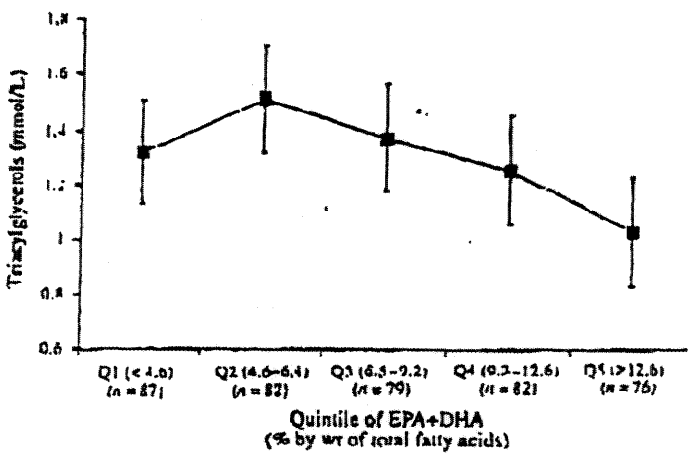

FIGURE 3. Mean (and 95% CI) concentrations of triacylglycerols according to quintile of eicosapentaenoic plus docosahexaenoic acid (EPA+DHA) concentrations in plasma phospholipids. *P* for trend = 0.03.

the general Quebec population during the same period (73). Considering the high prevalence of obesity and cigarette smoking in this population, which are known risk factors for high blood pressure (74, 75), it can be considered that the Inuit diet contributes to the low prevalence of high blood pressure in this population.

The effect of n−3 fatty acids on glycemia, insulinemia, and type 1 and 2 diabetes is not clear (76–78). n−3 Fatty acids may play a role in enhancing glucose metabolism, insulin secretion, and insulin receptor sensitivity (79–81). In this study, n−3 fatty acids were positively associated with plasma glucose, whereas an increase in EPA and the ratio of EPA to AA appeared to be inversely associated with plasma insulin. The prevalence of type 2 diabetes among native populations has been increasing in recent decades (21, 82–84). A sedentary lifestyle, the progressive abandoning of a traditional diet, an increasing intake of energy in the form of carbohydrates, and the high rates of obesity found in this population have favored this emergence (21, 85). Obesity is highly prevalent among the Inuit of Nunavik (86–88). Obese subjects (particularly those with abdominal obesity) are generally characterized by a cluster of metabolic disturbances including glucose intolerance, hyperinsulinemia, hypertriglyceridemia, low HDL-cholesterol concentrations, and an elevated ratio of total to HDL cholesterol (86, 89, 90). Our results agree with these findings (data not shown). Effectively, obese Inuit had higher values for these risk factors than did nonobese Inuit. However, as compared with obese Quebecers, obese Inuit had higher concentrations of n−3 fatty acids and HDL cholesterol and lower concentrations of insulin and triacylglycerols and a lower ratio of total to HDL cholesterol (91). Hence, these results suggest that n−3 fatty acids may attenuate metabolic disorders in obese subjects.

Kromhout et al (9) reported that mortality rates for arterial diseases were ≈50% lower among Dutch who consumed ≥30 g fish/d than among those who consumed no fish. In 1992–1996, the age-standardized mortality rate (per 100000 person years) for IHD [codes 410–414 in the 9th revision of the *International Classification of Diseases* (92)] was 66.3 for the Nunavik Inuit compared with 140.2 for the entire province of Quebec (93). Plasma phospholipid concentrations of EPA and DHA are higher in the Inuit than in Quebecers (geometric mean of EPA+DHA = 1.70; 95% CI: 1.67, 1.72) (91). Marine food intake by the Inuit was 131 g the day before the survey, corresponding to an intake of ≈2115 mg EPA+DHA. During the same period, the customary diet of Quebecers included ≈13 g fish/d (≈170 mg EPA+DHA), close to the mean daily intake in a typical US diet (between 100 and 200 mg) (17, 91, 94). Therefore, the lower IHD mortality rate observed in the Inuit population than in the general Quebec population suggests that the Inuit diet may contribute substantial benefits regarding cardiovascular health.

Despite the high prevalence of obesity and smoking among the Inuit of Nunavik, the mortality rate of IHD is low in this population, most likely because of their traditional diet rich in n−3 fatty acids. Our study showed some benefits of n−3 fatty acids (derived from marine sources) on CVD risk, notably, increased HDL-cholesterol and reduced triacylglycerol concentrations. However, evidence points to decreasing traditional food consumption by younger Inuit. Thus, the promotion of safe nutritional habits among Inuit presents a 2-fold challenge: maintain or increase traditional food use, which confers a comparative advantage to the Inuit population (eg, low IHD mortality rate), and support efforts to increase the use of healthy market foods.

We are grateful to Santé Québec for providing the databases of the health survey conducted among the Inuit of Nunavik and to Christopher Furgal for reviewing the manuscript.

REFERENCES

1. Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis. Lancet 1978;2:117–9.
2. Yamori Y, Nara Y, Iritani N, Workman RJ, Inegami T. Comparison of serum phospholipid fatty acids among fishing and farming Japanese populations and American islanders. J Nutr Sci Vitaminol (Tokyo) 1985;31:417–22.
3. Harris WS. Fish oils and plasma lipid and lipoprotein metabolism in humans: a critical review. J Lipid Res 1989;30:785–807.
4. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. JAMA 1998;279:23–8.
5. Hojo N, Fukushima T, Isobe A, et al. Effect of serum fatty acid composition on coronary atherosclerosis in Japan. Int J Cardiol 1998;66:31–8.
6. Connor WE. Importance of n−3 fatty acids in health and disease. Am J Clin Nutr 2000;71(suppl):171S–5S.
7. Oomen CM, Feskens EJM, Rasanen L, et al. Fish consumption and coronary heart disease mortality in Finland, Italy, and the Netherlands. Am J Epidemiol 2000;151:999–1006.
8. Bang H, Dyerberg J, Hjorne N. The composition of food consumed by Greenland Eskimos. Acta Med Scand 1976;200:69–73.
9. Kromhout D, Bosschieter EB, Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985;312:1205–9.
10. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989;2:757–61.
11. Shekelle RB, Missel L, Paul O, Shryock AM, Stamler L. Fish consumption and mortality from coronary heart disease. N Engl J Med 1985;313:820 (letter).
12. Schmidt EB, Skou HA, Christensen JH, Dyerberg J. N−3 fatty acids from fish and coronary artery disease: implications for public health. Public Health Nutr 2000;3:91–8.
13. Simon J, Hodgkins M, Browner W, Neuhaus J, Bernert J, Hulley S. Serum fatty acids and the risk of coronary heart disease. Am J Epidemiol 1995;142:469–76.
14. Leng GC, Taylor GS, Lee AJ, Fowkes FG, Horrobin D. Essential fatty acids and cardiovascular disease. The Edinburgh Artery Study. Vasc Med 1999;4:219–26.
15. Makivik Corporation B. The people and territory of Nunavik. Version current 18 May 2001. Internet: http://www.makivik.org/eng/backgrounders/people.htm (accessed 16 Jul 2001).
16. Hodgins S. Health and what affects it in Nunavik: how is the situation changing? Nunavik Regional Board of Health and Social Services, Koujjuaq, Canada: Bibliothèque nationale du Canada, 1997:7–18.
17. Kris-Etherton PM, Shaffer Taylor D, Yu-Poth S, et al. Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr 2000;71(suppl):179S–88S.
18. Santé Québec. Report of the Santé Québec Health Survey among the Inuit of Nunavik (1992). diet, a health determining factor. Montréal. Ministère de la Santé et des Services Sociaux, Gouvernement du Québec, 1995:47–124.
19. Blanchet C, Dewailly E, Ayotte P, Bruneau S, Receveur O, Holub BJ. Contribution of selected traditional and market foods in the diet of Nunavik Inuit women. Can J Diet Pract Res 2000;61:50–9.
20. Ebbesson SO, Schraer C, Nobmann ED, Ebbesson LO. Lipoprotein profiles in Alaskan Siberian Yupik Eskimos. Arctic Med Res 1996;55:165–73.
21. Brassard P, Rubinson L, Lavallée C. Prevalence of diabetes mellitus among the James Bay Cree of Northern Quebec. Can Med Assoc J 1993;149:303–7.

22. Robinson E. The health of the James Bay Cree. Can Fam Physician 1988;34:1606–13.
23. Welty TK, Lee ET, Yeh J, et al. Cardiovascular disease risk factors among American Indians: The Strong Heart Study. Am J Epidemiol 1995;142:269–87.
24. Santé Québec. Methods. In: Report of the Santé Québec Health Survey among the Inuit of Nunavik (1992). Montréal: Ministère de la Santé et des Services Sociaux du Québec, Gouvernement du Québec, 1994:17–33.
25. US Department of Health, Education, and Welfare. Lipid and lipoprotein analysis: manual of laboratory operation. Lipid Research Clinics Program. Washington, DC: US DHEW, 1982.
26. Després JP, Lamarche B, Mauriège P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 1996;334:952–7.
27. Holub BJ, Bakker DJ, Skeaff CM. Alterations in molecular species of cholesterol esters formed via plasma lecithin-cholesterol acyltransferase in human subjects consuming fish oil. Atherosclerosis 1987;66:11–8.
28. Logan A. Report of the Canadian Hypertension Society's consensus conference on the management of mild hypertension. Can Med Assoc J 1984;131:1053–7.
29. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Després JP. A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. Am J Clin Nutr 1996;64:685–93.
30. National Institutes of Health. Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults—the evidence report. Obes Res 1998;6(suppl):51S–209S.
31. Després JP, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 1990;10:497–511.
32. Pouliot MC, Després JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994;73:460–8.
33. Dewailly E, Ayotte P, Blanchet C, et al. Weighing contaminant risks and nutrient benefits of country food in Nunavik. Arctic Med Res 1996;55:13–9.
34. Bjerve K, Brubaak AM, Fougner K, Johnsen H, Midthjell K, Vik T. Omega-3 fatty acids: essential fatty acids with important biological effects, and serum phospholipid fatty acids as markers of dietary ω3-fatty acid intake. Am J Clin Nutr 1993;57(suppl):801S–6S.
35. SAS Institute Inc. The SAS system for Windows: the 6.12 edition. Cary, NC: SAS Institute Inc, 1996.
36. Bjerregaard P, Mulvad G, Pedersen HS. Cardiovascular risk factors in Inuit of Greenland. Int J Epidemiol 1997;26:1182–90.
37. Rode A, Shephard RJ, Vloshinsky PE, Kuksis A. Plasma fatty acid profiles of Canadian Inuit and Siberian Ganasan. Arctic Med Res 1995;54:10–20.
38. Moffat M, Young TK. Nutritional patterns of Inuit in the Keewatin region of Canada. Arctic Med Res 1994;53:298–300.
39. Kuhnlein H, Soueida R, Receveur O. Dietary nutrient profiles of Canadian Baffin Island Inuit by food source, season, and age. J Am Diet Assoc 1996;96:155–62.
40. Wein E, Freeman MMR, Makus JC. Use and preference for traditional foods among the Belcher Island Inuit. Arctic 1996;49:256–64.
41. Young TK, Gerrard JM, O'Neil JD. Plasma phospholipid fatty acids in the central Canadian Arctic: biocultural explanations for ethnic differences. Am J Phys Anthropol 1999;109:9–18.
42. Muckle G, Ayotte P, Dewailly É, Jacobson SW, Jacobson JL. Determinants of polychlorinated biphenyls and methylmercury exposure in Inuit women of childbearing age. Environ Health Perspect (in press).
43. Willett W. Food frequency methods. In: Willett W, ed. Nutritional epidemiology. 2nd ed. Monographs in epidemiology and biostatistics. Vol 30. New York: Oxford University Press, 1998:74–100.
44. Dewailly E, Bruneau S, Laliberté C, et al. The contaminants. In: Report of the Santé Québec Health Survey among the Inuit of Nunavik (1992). Montreal: Ministère de la Santé et des Services Sociaux, Gouvernement du Québec, 1994:73–107.
45. Parkinson AJ, Cruz AL, Heyward WL, et al. Elevated concentrations of plasma ω-3 polyunsaturated fatty acids among Alaskan Eskimos. Am J Clin Nutr 1994;59:384–8.
46. Schaeffer EJ, Lichtenstein AH, Lamon-Fava S, et al. Effects of National Education Program Step 2 diets relatively high or relatively low in fish-derived fatty acids on plasma lipoproteins in middle-aged and elderly subjects. Am J Clin Nutr 1996;63:234–41.
47. Jacobs DRJ, Mebane IL, Bangdiwala SI, Criqui MH, Tyroler HA. High density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: the follow-up study of the Lipid Research Clinics Prevalence Study. Am J Epidemiol 1990;131:32–47.
48. Tenkanen L, Pietila K, Manninen V, Mantarri M. The triglyceride issue revisited: findings from the Helsinki Heart Study. Arch Intern Med 1994;154:2714–20.
49. Castelli WP. The triglyceride issue: a view from Framingham. Am Heart J 1986;112:432–7.
50. Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. Fasting triglyceride, high-density lipoprotein and risk of myocardial infarction. Circulation 1997;96:2520–5.
51. Bulliyya G, Reddy KK, Reddy GP, Reddanna P, Kumari KS. Lipid profiles among fish-consuming coastal and non-fish-consuming inland populations. Eur J Clin Nutr 1990;44:481–5.
52. Gordon DJ. Factors affecting high-density lipoproteins. Endocrinol Metab Clin North Am 1998;27:699–709.
53. Castelli WP, Wilson PW, Levy D, Anderson K. Cardiovascular risk factors in the elderly. Am J Cardiol 1989;63:12H–9H.
54. Rifkind BM, Segal P. Lipid Research Clinics Program reference values for hyperlipidemia and hypolipidemia. JAMA 1983;250:1869–72.
55. Galli C, Simopoulos AP, Tremoli E, eds. Effects of fatty acids and lipids in health and disease. Proceedings of the 1st International Congress of the International Society for the Study of Fatty Acids and Lipids (ISSFAL). Lugano, Switzerland, June 30-July 3, 1993. World Rev Nutr Diet 1994;76:1–152.
56. Kestin M, Clifton P, Belling GB, Nestel PJ. n−3 Fatty acids of marine origin lower systolic blood pressure and triglycerides but raise LDL cholesterol compared with n−3 and n−6 fatty acids from plants. Am J Clin Nutr 1990;51:1028–34.
57. Nestel PJ. Fish oil and cardiovascular disease: lipids and arterial function. Am J Clin Nutr 2000;71(suppl):228S–31S.
58. Sanchez-Muniz FJ, Bastida S, Viejo JM, Terpstra AHM. Small supplements of n−3 fatty acids change serum low density lipoprotein composition by decreasing phospholipid and apolipoprotein B concentrations in young adult women. Eur J Nutr 1999;38:20–7.
59. Mori TA, Burke V, Puddey IB, et al. Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. Am J Clin Nutr 2000;71:1085–94.
60. Contacos C, Barter PJ, Sullivan DR. Effect of pravastatin and omega-3 fatty acids on plasma lipids and lipoproteins in patients with combined hyperlipidemia. Arterioscler Thromb 1993;13:1755–62.
61. Suzukawa M, Abbey M, Howe PR, Nestel PJ. Effects of fish oil fatty acids on low density lipoprotein size, oxidizability, and uptake by macrophages. J Lipid Res 1995;3:473–84.
62. Foulon T, Richard MJ, Payen N, et al. Effects of fish oil fatty acids on plasma lipids and lipoproteins and oxidant-antioxidant imbalance in healthy subjects. Scand J Clin Lab Invest 1999;59:239–48.
63. Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, Ganz P. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. N Engl J Med 1995;332:488–93.
64. Hansen J, Pedersen H, Mulvad G. Fatty acids and antioxidants in the Inuit diet. Their role in ischemic heart disease (IHD) and possible interactions with other dietary factors. A review. Arctic Med Res 1994;53:4–17.

65. Salonen JT, Nyyssonen K, Korpela H, Tuomilehto J, Seppanen R, Salonen R. High stored iron levels are associated with excess risk of myocardial infarction in Eastern Finnish men. Circulation 1992;86: 803–11.
66. Morel DW, DiCorleto PE, Chisolm GM. Endothelial and smooth muscle cells alter low density lipoprotein in vitro by free radical oxidation. Arteriosclerosis 1984;4:357–64.
67. Suadicani P, Hein HO, Gyntelberg F. Serum selenium concentration and risk of ischaemic heart disease in a prospective cohort study of 3000 males. Atherosclerosis 1992;96:33–42.
68. Salonen JT. Association between cardiovascular death and myocardial infarction and serum selenium in a matched-pair longitudinal study. Lancet 1982;24:175–9.
69. Morris MC, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. Circulation 1993;88:523–33.
70. Conquer J, Cheryk L, Chan E, Gentry P, Hulub B. Effect of supplementation with dietary seal oil on selected cardiovascular risk factors and hemostatic variables in healthy male subjects. Thromb Res 1999;96:239–50.
71. Platen H, Hostmark AT, Kierulf P, et al. Fish-oil concentrate: effects on variables related to cardiovascular disease. Am J Clin Nutr 1990; 52:300–6.
72. Ryu J, Lerner J, Sullivan J. Unresponsiveness of forearm hemodynamics to omega-3 polyunsaturated fatty acids and aspirin. Prostaglandins 1990;39:339–47.
73. Santé Québec. Et votre coeur, ça va? Rapport de l'enquête québécoise sur la santé cardiovasculaire 1990. (Report on cardiovascular health in the Quebec population, 1990.) Montréal: Ministère de la Santé et des Services Sociaux, Gouvernement du Québec, 1994 (in French).
74. Kannel WB. Fifty years of Framingham Study contributions to understanding hypertension. J Hum Hypertens 2000;14:83–90.
75. Wilson PW. An epidemiologic perspective of systemic hypertension, ischemic heart disease, and heart failure. Am J Cardiol 1997; 80:3J–8J.
76. Landgraf R. N−3 fatty acids in diabetes mellitus. In: Frolich JC, von Schacky C, eds. Fish, fish oil and human health. Munich, Germany: W Zuckschwerdt Verlag, 1992:123–34.
77. Hendra TJ, Britton ME, Roper DR, et al. Effects of fish oil supplements in NIDDM subjects. Controlled study. Diabetes Care 1990; 13:821–9.
78. Axelrod L. Omega-3 fatty acids in diabetes mellitus: gift from the sea. Diabetes 1989;38:539–43.
79. Clarke SD. Polyunsaturated fatty acid regulation of gene transcription: a mechanism to improve energy balance and insulin resistance. Br J Nutr 2000;83(suppl):S59–66.
80. Storlien LH, Kriketos AD, Calvert GD, Baur LA, Jenkins AB. Fatty acids, triglycerides and syndromes of insulin resistance. Prostaglandins Leukot Essent Fatty Acids 1997;57:379–85.
81. Lardinois CI. The role of omega-3 fatty acids on insulin secretion and insulin sensitivity. Med Hypotheses 1987;24:243–8.
82. Scheuer C, Adler A, Mayer A, Halderson K, Trimble B. Diabetes complications and mortality among Alaska Natives: 8 years of observation. Diabetes Care 1997;20:314–21.
83. Greenlund J, Valdez R, Casper M. Prevalence and correlates of the insulin resistance syndrome among Native Americans. Diabetes Care 1999;22:441–7.
84. Ellis JL. Cardiovascular disease risk factors in Native Americans: a literature review. Am J Prev Med 1994;10:295–307.
85. Ebbesson SO, Kennish J, Ebbesson L, Go O, Yeh J. Diabetes is related to fatty acid imbalance in Eskimos. Int J Circumpolar Health 1999;58:108–19.
86. Lamarche B, Tchernof A, Mauriège P, et al. Fasting insulin and apolipoprotein B levels and low-density lipoprotein particle size as risk factors for ischemic heart disease. JAMA 1998;279: 1955–61.
87. Yarnell JWG, Sweetnam PM, Marks V, Teale JD, Bolton CH. Insulin in ischaemic heart disease: are associations explained by triglyceride concentrations? The Caerphilly Prospective Study. Br Heart J 1994;71:293–6.
88. Pyörälä K. Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. Diabetes Care 1979;2:131–41.
89. Després JP. Abdominal obesity and the risk of coronary artery disease. Can J Cardiol 1992;8:561–2.
90. Pouliot MC, Després JP, Nadeau A, et al. Visceral obesity in men: associations with glucose tolerance, plasma insulin, and lipoprotein levels. Diabetes 1992;41:826–34.
91. Dewailly E, Blanchet C, Gingras S, et al. Relations between n−3 fatty acid status and cardiovascular disease risk factors among Quebecers. Am J Clin Nutr (in press).
92. World Health Organization. International classification of diseases, ninth revision (ICD-9). Geneva: WHO, 1977.
93. Ministère de la santé et des services Sociaux du Québec. Surveillance de la mortalité au Québec: Année 1992–1996. (Mortality surveillance in Quebec, 1992–1996.) Québec: Gouvernement du Québec, 1998 (in French).
94. Rayet NR, Cronin JF, Exler J. Omega-3 fatty acid content of the US food supply. J Am Coll Nutr 1992;11:304–8.